that associated endomyocardial disease occurs if a substantial number of eosinophils are degranulated. Though special staining may show these abnormal cells at histological examination, degranulation may be so severe that assessment of the abnormal cells can only be made at electronmicroscopical level. This has been my experience in isolated cases.

Electronmicroscopical evaluation has also been undertaken on cardiac tissue in assessing prognosis in patients with dilated (congestive) cardiomyopathy.^{10 11} Degrees of hypertrophy can also be more accurately assessed.¹² It has also been used in an effort to find a morphological explanation for the clinical manifestations of hypertrophic cardiomyopathy,¹³ though its diagnostic value at that level of investigation is controversial.¹⁴

So far as primary diagnosis is concerned examination by electron microscopy alone is of limited value. Even so, in combination with light microscopical examination, this level of morphological analysis can be of great value; the electron microscope should now be accepted as an important component in routine pathology laboratories.

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Regular Review

Primary biliary cirrhosis

D R TRIGER

Until recently primary biliary cirrhosis was considered to be a rare disorder characterised by chronic cholestasis, pigmentation, xanthomatous eruptions, and histological features of chronic non-suppurative destructive cholangiohepatitis. The classic presenting feature is generalised pruritus in a middle-aged woman, usually preceding jaundice; and the disorder is then chronic and progressive, leading to death from liver failure or the complications of portal hypertension within five to seven years. With the discovery of the antimitochondrial antibody and its diagnostic specificity in liver disease, however, the disease has acquired a broader aspect. Many cases lack both the typical clinical and histological features. Indeed, primary biliary cirrhosis is now being diagnosed with increasing frequency, and in many English liver clinics it is arguably the most common cause of cirrhosis in middle-aged and elderly women. This observation prompted several epidemiological studies which formed the basis of a workshop reported in a leading article in the *BMJ* last year.¹ Interest has been further aroused by a report that environmental factors might play a part in the pathogenesis of primary biliary cirrhosis,² and a multinational inquiry into the incidence and prevalence of the

disease is being mounted^{2a} in the hope that it may help to shed light on its aetiology.

The two laboratory abnormalities most commonly associated with primary biliary cirrhosis are a raised serum alkaline phosphatase activity and a positive antimitochondrial antibody test result. As requests for routine biochemical and auto-immune profiles have become more common many patients are being found to have early presymptomatic liver disease.³ Some patients have even been described with unequivocal histological evidence of primary biliary cirrhosis in whom serum bilirubin, alkaline phosphatase, and transaminase values were entirely normal, though in most such cases abnormalities could be found in serum IgM and gammaglutamyltransferase. On the other hand, several groups have reported asymptomatic patients with the presence of serum antimitochondrial antibody and no biochemical or histological evidence of primary biliary cirrhosis.⁴⁻⁶ Presumably many of these patients may ultimately develop the clinical disease which we recognise as primary biliary cirrhosis, but the rate at which this occurs is highly variable, and the stimuli initiating this process are unknown. Our present knowledge suggests that genetic, infective,

immunological, and environmental factors need to be considered as possible precipitating agents. Prospective studies of such patients may well provide important clues to the triggering mechanisms—but a major obstacle in such studies will inevitably be the poor correlation between clinical symptoms and liver damage seen both in primary biliary cirrhosis and in other chronic liver diseases.

Despite the diagnostic specificity of antimitochondrial antibodies in clinical liver disease, their presence in other clinical settings raises important questions about their nature and significance. Most laboratories test for antimitochondrial antibodies by an indirect immunofluorescence technique using a polyvalent immunoglobulin conjugate and rat liver, kidney, and stomach as substrate tissue. There is no universally accepted standard technique, but in most patients with primary biliary cirrhosis the antibody is present in a titre of 1/80 or greater. Even in the so-called negative antimitochondrial patients the antibody can usually be detected in undiluted serum.⁷ Other techniques have been used, such as complement fixation, double immunodiffusion, and fluorescence immunoassay, and it appears that mitochondrial antibodies comprise a heterogeneous range.⁸ Specific antibodies to fractions of the mitochondria can be defined, and they can be further modified chemically by agents such as trypsin. Our understanding of primary biliary cirrhosis should be advanced by further characterisation of these submitochondrial particles and the correlation of the antibody types with clinical and histological features. It remains to be seen whether the antibody of the presymptomatic patients with little or no histological evidence of liver disease shows the same pattern as that seen in patients with true primary biliary cirrhosis.

Other immunological phenomena are associated with primary biliary cirrhosis, though whether they are directly concerned in the pathogenesis or merely reflect a response to the pathological process is still not clear. Many patients with primary biliary cirrhosis can be shown to form immune complexes⁹ and abnormalities in complement metabolism,¹⁰ and the severity of inflammatory activity around the portal tracts correlates with the level of circulating complexes as do the serum concentrations of IgG and IgM.¹¹ Though the primary lesion in primary biliary cirrhosis affects the bile ducts, many patients have evidence of systemic disturbances in the form of the CRST syndrome (calcinosis, Raynaud's, sclerodactyly, telangiectasia),¹² Sjögren's syndrome,¹³ thyroid disease,¹⁴ and pancreatic hyposecretion.¹⁵ Though these may be the result of a generalised autoimmune process, an alternative explanation for at least some of the disorders might be that they are the clinical manifestation of deposited immune complexes. The complexes in primary biliary cirrhosis are thought to be much larger than in other liver diseases and to contain predominantly IgM. This is consistent with the observation that the extrahepatic phenomena seen in patients with primary biliary cirrhosis are different from those seen in other liver disorders. The skin has been shown to be a common site of deposition of IgM and complement in primary biliary cirrhosis.¹⁶ The part played by immunoglobulins and immune complexes in the lichenoid reactions and other dermatological conditions seen in patients with primary biliary cirrhosis (with and without treatment with penicillamine) awaits further elucidation. No satisfactory explanation has yet been offered for the observation that over 70% of patients with primary biliary cirrhosis have raised serum concentrations of IgM. Though the immunoglobulin concentration tends to rise with progression of the disease, raised concentrations are frequently seen in presymptomatic patients, and there are no clinical or

histological features distinguishing patients with normal concentrations of IgM from those in whom these are raised. Though D-penicillamine reduces the serum IgM concentration in the first few months of treatment, this reduction is probably not sustained.

Progress has also been made in respect of treatment. Two distinct but important approaches exist: that directed towards the complications of the disease, and more specific measures aimed at the disease itself. Osteomalacia is an important extrahepatic complication, though it presents a major clinical problem only rarely. A recent claim that it can be reversed with comparatively small doses of vitamin D₃¹⁷ suggests that it is due to malabsorption of the vitamin secondary to chronic cholestasis rather than to defective liver hydroxylation or to tissue resistance to 1,25-dihydroxy vitamin D₃. Since many patients are elderly inadequate nutrition is often an additional factor predisposing to osteomalacia. Osteoporosis is more difficult to treat, and the reason for its frequent occurrence in primary biliary cirrhosis is uncertain; possible factors include malabsorption of calcium, phosphate, and vitamin D as well as oestrogen withdrawal, as it is most apparent after the menopause. Recently it has been shown that thinning of cortical bone can be reversed by calcium supplements in the form of microcrystalline hydroxyapatite compound.¹⁸ If confirmed, this treatment offers hope for a particularly troublesome chronic complaint.

Accumulation of copper in the liver has been known for many years to be a feature of primary biliary cirrhosis.¹⁹ It probably occurs as a consequence of chronic cholestasis, and its presence is unlikely to be the initiating pathogenetic factor in the liver disease. By analogy with Wilson's disease, however, its excess in the liver may well be toxic (though the intracellular distribution is quite different, the copper being predominantly in the lysosomes in Wilson's disease and in the cytosol in primary biliary cirrhosis²⁰).

Attempts to treat the liver lesion itself have received much attention in recent years. Though never subjected to any long-term controlled trials, corticosteroids have not found favour, and they are probably contraindicated because of their undoubted tendency to aggravate osteoporosis. Azathioprine has no beneficial effect,²¹ but preliminary trials using D-penicillamine are showing some promising results. The copper-chelating properties on which the original rationale for using the drug was based are now thought to be less important than the anti-inflammatory and antifibrotic effects. The D-penicillamine reduces the amount of circulating immune complexes and produces a slight but definite reduction in serum transaminase activities. More specifically, the drug reduces active inflammation within the liver as judged from serial liver biopsy specimens.^{22 23} The effect on survival is less clear cut, some workers claiming an improvement using D-penicillamine,^{23 24} while others have abandoned the drug on the grounds that they have been unable to show any benefit and that the incidence and nature of the side effects limit its usefulness.²⁵

Many clinical trials are still in progress throughout Europe and North America, but already a pattern is emerging. Most studies use a daily dose of 500-900 mg, though doses as low as 250 mg have been advocated.²⁶ Side effects are so frequent that the dose must be modified in 20-30% of patients. Patients with very early disease may have such a good prognosis that many years' follow-up will be needed to show whether the drug has any beneficial effect. Indeed, the potential toxicity of penicillamine is such that its use may not be justifiable in these patients. On the other hand, those with very advanced liver disease are unlikely to benefit from the drug. They often die at

this stage because of long-established processes such as portal hypertension, which D-penicillamine can hardly be expected to modify. The many trials in progress should provide clinical guidance on the selection of patients for chemotherapy, but the variability in the rate of progression of the disease is such that studies will need to last at least five years to answer this question. In the mean time caution should be urged against overenthusiastic and uncritical use of this powerful drug, since at best it will delay and is most unlikely to reverse the progression of the disease. Doubts about its efficacy as an anti-fibrotic agent, coupled with the problems of side effects, have already led some workers to look for alternative therapeutic agents such as colchicine.

What can be done for other complications of primary biliary cirrhosis? Though bleeding from oesophageal varices usually implies advanced liver damage, patients with primary biliary cirrhosis sometimes present with catastrophic haemorrhage in the face of remarkably good hepatic function. The explanation is that some patients with primary biliary cirrhosis have presinusoidal portal hypertension in which the portal pressure may rise dramatically in the absence of cirrhosis. Such patients may benefit from decompression shunt surgery, and a five-year survival of 66% has been reported.²⁷ The older the patient, however, the greater the incidence of encephalopathy after portacaval shunt, and since most patients with primary biliary cirrhosis bleeding from varices are aged over 60 this procedure is of limited value. Oesophageal sclerotherapy offers an alternative and potentially attractive means of controlling this major complication in a group of patients who may do well for many years.

Recent advances offer hope even for patients dying with hepatic failure. MacDougall and colleagues²⁸ have suggested that patients with non-alcoholic cirrhosis are the most suitable candidates for liver transplantation, and, though many patients with primary biliary cirrhosis are too old for this to be considered, the published experience from Cambridge and Denver includes 16 cases of primary biliary cirrhosis with five patients surviving longer than one year.^{28 29} The anti-mitochondrial antibody disappears only transiently in survivors, perhaps implying that the factor responsible for the autoantibody is not primarily hepatic, and a recent report has suggested that the disease itself may recur in the transplanted liver despite the use of immunosuppressive drugs.³⁰ These preliminary data should be interpreted with some caution, since low-grade chronic rejection of the graft may produce a similar picture.³¹ There are many similarities between the histological process observed in graft-versus-host reactions and that seen in primary biliary cirrhosis.³² Here again there may be clues to the origin of the disease.

So, though fundamental questions about the pathogenesis of primary biliary cirrhosis remain unanswered, the recent surge of interest in both its clinical course and its treatment promises further progress in the not-too-distant future.

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